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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/810,700	03/16/2001	Michael K. Wong	00-149-US	7224

7590 04/14/2004

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/810,700	WONG ET AL	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-22* is/are pending in the application.

4a) Of the above claim(s) *21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 3-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 1, 7, 11 and 17 have been amended. Claim 2 has been canceled. Claims 1and 3-22 are pending. Claims 21 and 22, drawn to non-elected inventions, remain withdrawn from consideration. Claims 1 and 3-20 are under consideration.

2. The Notice of NonCompliant Amendment mailed August 11, 2003 is withdrawn.

3. The text of sections of title 35 U.S code not found in this action can be found in a previous action.

4. Claim 14 is objected to because of the following informalities: diphtheria is misspelled . Appropriate correction is required.

5. Claims 1, 3-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claim 1 recites "purified peptide fragment". It is unclear how "peptide fragment" differs from "peptide" and it is unclear what limitations are to be imposed on the larger polypeptide from which the "peptide fragment" is a subfragmented of.

(B) Claim 7 recites "group consisting essentially of". It is unclear how a "group consisting essentially of" differs from a "group consisting of".

(C) Claims 8 and 10. It is unclear how claims 8 and 10 further limit claim 7 because any peptide is "capable" of being further conjugated or fused to another molecule. Claim 8 does not recite any structural alteration of the recited peptides in claim 7 that would further limit claim 7.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1 and 3-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention..

Claim 1 is drawn to a purified peptide fragment with selective binding to tumor derived endothelial cells, wherein the peptide fragment possesses a charge motif of positive-positive-neutral hydrophobic, wherein the peptide fragment is not greater than fifty amino acid residues in length. Claim 3 embodies the purified peptide fragment of claim 1 wherein said peptide is operatively linked to a therapeutic agent capable of exerting a cytotoxic effect on a tumor. Claim 4 embodies the purified peptide fragment of claim 1 formulated as a pharmaceutical composition. Claim 5 embodies the purified peptide fragment of claim 1 wherein the peptide attached to a therapeutic agent is capable of exerting a cytotoxic effect on tumor vasculature sufficient to lead to tumor necrosis. Claim 6 embodies the purified peptide of claim 1 wherein said peptide fragment is linked to a diagnostic agent that is detectable upon imaging.

The claims are drawn to a genus of peptides which minimally comprise a three contiguous amino acid residues, where said three amino acids are positive, positive, neutral hydrophobic. The claim requires that said peptides have the functional attribute of selective-binding to tumor derived endothelial cells. The genus of claimed proteins is highly variant because numerous structural alterations are tolerated in members of the genus which has the structural limitation of comprising only three required amino acids. Numerous functional attributes are also tolerated in members of the genus because the limitation "binding to tumor derived endothelial cells" reads on binding to any subcomponent of tumor derived endothelial cells, such as those taught by Epstein et al (WO 90/03801)to be fibronectin, laminin and type IV collagen (page 14, lines 18-24), as well as binding to any antigen which is selectively expressed in the vicinity of a tumor such as cell adhesion molecules responsible for adherence of PMN leukocytes, fibrin, fibrin degradation products and fibronectin (page 14, line 32 to page 15, line 3), the receptors flk and kdr, and heparin-containing proteoglycans as taught by Senger et al (US 6,022,541, column 6, lines 48-52), as well as the TIE2/Tek as taught by the abstract of Peters et al (British Journal of Cancer, 1998, Vol. 77, pp. 51-56). the instant specification describes SEQ

ID NO:1-5 as having the claimed sequence motif and property of binding to tumor-derived endothelium. These sequences do not adequately describe the claimed genus, because the genus includes peptides which bind to numerous sub-endothelial components and antigens which are selectively accessible on, or selectively expressed by tumor associated endothelium. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus.

It is noted that a structural element in addition to the positive-positive-neutral hydrophobic motif is present in SEQ ID NO:1-5, namely a cysteine residue at the amino and carboxyl terminus, and a palindrome-type sequence surrounding the three amino acid motif, such that there is symmetry surrounding the three amino acid sequence and the ends of said sequence can form a disulfide bridge. It appears that the instant peptides would be structurally constrained by the cysteine bonds and that the "reflected" sequence on either side of the claimed three amino acid sequence (CGG---GGC) and (CLL----LLC) would impart a particular structure to the sequences beyond that of the simple three amino acid sequence. Applicant is encourage to claimed the genus of proteins with more structural specificity

8. Claims 1 and 3-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (WO 00/04052).

The specific embodiments of the claims are recited above.

Smith et al disclose a pharmaceutical composition for treating a established primary tumor and for preventing the growth of secondary tumors following surgery (page 15, lines 24-26). Smith et al disclose that said composition comprise structure which comprise anti-angiogenic agents linked to a peptidic membrane binding entity (page 4, lines 2-10). Smith et al teach a specific peptidic membrane binding entities which are SEQ ID NO:12 (page 4, line 26 to page 5, line 3). SEQ ID NO:12 contains "Lsy-Arg-Phe", and SEQ ID NO:13 and 14 contain "Lys-Lys-Ser" which fulfill the limitation of claim 1 with respect to the claimed binding motif of positive-positive-neutral hydrophobic. Smith et al disclose that the membrane binding element associated with the anti-angiogenic peptide has affinity for the vascular endothelium of growing vessels (page 2, lines 20-24, and abstract, lines 1-3). Smith et al disclose that the membrane binding elements have low affinities for membrane components but high affinities for blood vessel endothelium (page 2 line 30 to page 3, line 2). Smith et al do not specifically state that the

anti-angiogenic agent attached to the membrane binding element is capable of inducing tumor necrosis. However, an anti-angiogenic agent inhibits the formation of new blood vessels at the tumor site, thus depriving the growing tumor of oxygen and nutrients. Smith et al discloses the administration of the angiogenesis -inhibiting agent comprising the peptidic binding elements for treating a established primary tumor. It would be inherent in this treatment that the growing tumor would undergo necrosis because it would be deprived of an increasing supply of oxygen and nutrients.

9. Claims 1 and 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (WO 00/04052) in view of Epstein (WO 90/03801). The specific embodiments of the claims 1are set forth above.

Smith et al teach the peptides of SEQ ID NO:12-14 which are linked to anti-angiogenic agents for the treatment of primary tumors or metastatic tumors after removal of said primary tumor. Smith et al do not teach a diagnostic agent that is detectable upon imaging linked to SEQ ID NO:12-14.

Epstein et al teach a delivery vehicle having the ability to concentrate at the site of neoplastic tissue wherein said delivery vehicle is conjugated to a tumor imaging agent (page 9, lines 32-35). Epstein et al teach delivery vehicles having specificity for sub-endothelial components of the blood vessel wall that become accessible in structurally abnormal endothelium associated with tumors (page 14, lines 18-24) Epstein et al also teach delivery vehicles that bind to antigens selectively expressed upon tumor associated endothelial cells (page 14, line 34 to page 15, line 3).

It would have been prima facie obvious at the time the invention was made to link the peptidic membrane binding elements as taught by Smith et al to have high affinity for tumor endothelium to a tumor imaging agent as taught by Epstein et al. One of skill in the art would have been motivated to do so by the teachings of Epstein et al on the concentration of tumor imaging agents at the site of the neoplastic tissue by agents having affinity for vascular endothelium associated with tumors.

10. Claims 1 and 4 are rejected under 35 U.S.C. 102(a) as being anticipated by Oku et al (WO 00/23476).

Oku et al disclose SEQ ID NO:3 which has the claimed sequence motif of "Arg-His-Val" in a 15-mer amino acid sequence (page 2 of the sequence listing). The abstract of Oku et al teach that SEQ ID NO:3 is a neovascular-specific peptide. The abstract teaches that the disclosed peptide is useful for the treatment and diagnosis of cancer. Because the peptide is a neovascular-specific peptide it will bind to tumor endothelium that is developing as a result of angiogenesis and fulfill the specific embodiment of claim 1 with regard to selective binding to tumor derived endothelial cells.

11. Claims 1 and 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epstein (WO 90/03801) in view of Oku et al (WO 00/23476).

Epstein et al teach conjugates of delivery vehicles having the ability to locate at neoplastic sites (page 13, lines 20-23). Epstein et al teach delivery vehicles that have specificity for components of the endothelium that become accessible in tumor endothelium (page 14, lines 18-24) and delivery vehicles with specificity for antigens selectively expressed in vascular tissue in the vicinity of tumors (page 14 lines 32 to page 15, line 2). Epstein et al teach a delivery vehicle having the ability to concentrate at the site of neoplastic tissue wherein said delivery vehicle is conjugated to a tumor imaging agent (page 9, lines 32-35). Epstein et al do not teach a delivery vehicle having the claimed sequence motif which is not greater than fifty amino acid residues.

Oku et al teach SEQ ID NO:13 binds specifically to neovascular endothelium. (abstract). SEQ ID NO:3 has the claimed motif of "Arg-His-Val" in a 15-mer amino acid sequence (page 2 of the sequence listing). the abstract teaches that the disclosed peptide is useful for the treatment and diagnosis of cancer.

It would have been prima facie obvious at the time the claimed invention was made to substitute the peptide taught by Oku et al for a delivery vehicle taught by Epstein et al. One of skill in the art would have been motivated to do so by the teachings of Oku et al that SEQ ID NO: 3 binds to neovascular endothelium. Because the peptide is a neovascular-specific peptide it will bind to tumor endothelium that is developing as a result of angiogenesis and fulfill the

specific embodiment of claim 1 with regard to selective binding to tumor derived endothelial cells., and thus fulfill the criteria of Epstein et al on a delivery vehicle to tumor derived endothelium.

12. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments and arguments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
Art Unit 1642
04/09/04

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PRIMARY EXAMINER